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ARIOSA DIAGNOSTICS, INC.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

VERINATA HEALTH, INC.,

Plaintiff and Counterclaim-Defendant,

v.

ARIOSA DIAGNOSTICS, INC.,

Defendant and Counterclaim-Plaintiff.

ILLUMINA, INC.,

Plaintiff and Counterclaim-Defendant

v.

ARIOSA DIAGNOSTICS, INC.,

Defendant and Counterclaim-Plaintiff.

Lead Case No. 3:12-cv-05501-SI
Case No. 3:14-cv-01921-SI
Case No. 3:15-cv-02216-SI

ARIOSA DIAGNOSTICS INC.'S NOTICE OF MOTION, MOTION, AND MEMORANDUM OF POINTS AND AUTHORITIES IN SUPPORT OF ITS MOTION TO PRECLUDE THE TESTIMONY OF GREGORY COOPER, Ph.D.

Judge: Hon. Susan Illston

Date: October 12, 2017
Time: 10:00 am.
Ctrm.: 1, 17th Floor

ILLUMINA, INC.,

Plaintiff and Counterclaim-Defendant

v.

ARIOSA DIAGNOSTICS, INC.,

Defendant and Counterclaim-Plaintiff.

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NOTICE OF MOTION AND MOTION

PLEASE TAKE NOTICE that on October 12, 2017 at 10:00 a.m., or as soon thereafter as counsel may be heard, in Courtroom 1 of the United States District Court for the Northern District of California, San Francisco Division, located at 450 Golden Gate Avenue, 17th Floor, San Francisco, California, Defendant Ariosa Diagnostics, Inc. ("Ariosa") will and hereby does move this Court for an order precluding portions of the Corrected Opening Expert Report of Dr. Gregory Cooper ("expert report"), served on June 27, 2017, and precluding any testimony in reliance thereon as set forth in the Memorandum of Points and Authorities. This motion is supported by the accompanying Memorandum of Points and Authorities, the Declaration of Sandra L. Haberny and accompanying exhibits, the pleadings and papers on file in this action, other matters of which this Court may take judicial notice, and any further evidence and argument that may be presented at or before any hearing on this matter.

MEMORANDUM OF POINTS AND AUTHORITIES

Ariosa moves to preclude Plaintiffs' technical expert Dr. Gregory Cooper from offering the opinion set forth in paragraphs 240-244 of his expert report and in related deposition testimony on at least the ground that it is speculative and unreliable, and contrary to the requirements of Federal Rule of Evidence 702. The district court acts as a gatekeeper to exclude expert testimony that does not satisfy the relevancy and reliability requirements of Federal Rule of Evidence 702. *Estate of Barabin v. AstenJohnson, Inc.*, 740 F.3d 457, 467 (9th Cir. 2014) (*en banc*); *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589 (1993). Dr. Cooper's opinion in paragraphs 240-244, and related testimony, is based on nothing more than a speculative "guess," for which Dr. Cooper admitted in his deposition he has no reliable basis.

In *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, the Supreme Court held that reliable testimony must be grounded in the methods and procedures of science and signify something beyond "subjective belief or unsupported speculation." 509 U.S. at 590. The Supreme Court delineated four factors to determine the reliability of expert testimony: (1) the testability of the expert's hypothesis; (2) whether the theory or technique has been subject to peer review and publication; (3) the known or potential rate of error; and (4) whether the technique is generally

accepted. *Id.* at 592-94. While these factors are not exhaustive, they are representative of the types of evidence a trial court should look at to determine reliability. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 138, 158 (1999).

At paragraphs 240-244 of his report (and in related deposition testimony), Dr. Cooper offers an opinion in an attempt to show that Version 2 of the Harmony Prenatal Test ("Harmony V2") satisfies steps (a) and (b) of claim 1 of U.S. Patent No. 7,955,794 (the "'794 patent"). Ex. 2 (Cooper Rpt.) at ¶ 240;[1] *see also* Ariosa's concurrently-filed Motion for Summary Judgment, at Section V.A.4. As discussed below, this opinion seeks to overcome what, in reality, is an insurmountable problem for Illumina: Harmony V2 does not perform the steps of claim 1—and, in particular, steps (a) and (b)—in the recited order.

Claim steps 1(a) and (b) recite, in pertinent part:

> (a) providing a sample which may contain at least 100 different single-stranded target sequences attached to a first solid support;
>
> (b) contacting said target sequences with a probe set comprising more than 100 different single-stranded probes, wherein each of said more than 100 different probes comprises:
>
> > i) a first universal priming site, wherein each of said more than 100 different probes has identical universal priming sites, and
> >
> > ii) a target specific domain such that different double-stranded hybridization complexes are formed, each of the different hybridization complexes comprising one of said more than 100 different single-stranded probes and one of the different single-stranded target sequences from the sample;

As explained in Ariosa's concurrently-filed motion for summary judgment, at Section II.B.1, pp. 4-5, in Harmony V2, a sample of single-stranded cell-free DNA ("cfDNA") (allegedly

[1] "Ex." herein refers to exhibits to the Declaration of Sandra L. Haberny, filed concurrently with and in support of this Motion; Ariosa's Motion for Summary Judgment; Ariosa's Motion To Strike Portions Of Corrected Expert Report Of Gregory Cooper, Ph.D. and To Preclude Reliance Thereon; and Ariosa's Motion to Preclude the Testimony of James Malackowski.

the recited "single-stranded target sequences" introduced in step 1(a)) is biotinylated[2] and then mixed with DANSR oligos (allegedly the "single-stranded probes" introduced in step 1(b)). During a two-hour incubation period, the single-stranded cfDNA and single-stranded oligos form double-stranded hybridization complexes (allegedly the "double-stranded hybridization complexes" introduced in step 1(b)). After the double-stranded hybridization complexes are formed, streptavidin-coated beads (allegedly the "first solid support" introduced in step 1(a)) are added to the sample, and the double-stranded hybridization complexes become attached to the beads.

As is apparent from this description, Harmony V2 does not follow steps 1(a) and 1(b) in the order recited. Step 1(a) provides for a sample with single-stranded target sequences attached to a first solid support; and step 1(b) provides for contacting those single-stranded sequences attached to a first solid support with single-stranded probes thereby forming double-stranded hybridization complexes. By contrast, in Harmony V2, streptavidin-coated beads (which Illumina treats as the "first solid support") are added *after* an incubation period in which single-stranded cfDNA sequences form double-stranded hybridization complexes with single-stranded oligos. Accordingly, Harmony V2 does not follow steps 1(a) and 1(b) in the order recited because it does not (i) *first* provide a sample containing single-stranded target sequences already attached to a solid support and (ii) *then* contact the single-stranded target sequences attached to the first solid support with single-stranded probes thereby forming double-stranded hybridization complexes.

Dr. Cooper offers the opinion that Harmony V2 nevertheless satisfies steps 1(a) and 1(b) because these steps need not be performed in the recited order. As explained in Ariosa's Motion for Summary Judgment, this claim construction—offered for the first time in Dr. Cooper's expert report—is untenable under controlling Federal Circuit authority. No doubt recognizing this obstacle, Dr. Cooper offers an *alternative* opinion at paragraphs 240 through 244. That opinion is unreliable and should be excluded.

[2] "Biotinylation" refers to conjugating a "biotin" molecule onto the cfDNA. The biotin tag can later bind to a streptavidin molecule (its binding partner) coated onto a bead, such that the biotin-streptavidin interaction permits the cfDNA (and everything with which it is in complex) to be captured onto the bead.

Specifically, Dr. Cooper states in his report that some fraction of the single-stranded cfDNA sequences might not form hybridization complexes with the single-stranded oligos during the incubation period, leaving them available to become attached to the beads while they are still single-stranded. Ex. 2 (Cooper Rpt.) at ¶¶ 240-244; *id.* at ¶ 242. He contends that "*if*" some fraction of the single-stranded cfNDA sequences "fail to hybridize to their cognate probes, or hybridize to their cognate probes but then dissociate from them, within the 2 hours allowed by V2HPT for probe-target annealing," then the "target sequences would exist in single-stranded form when the SA beads are added to the mixture." *Id.* at ¶ 242.[3]

Dr. Cooper concedes that "[he] cannot estimate with precision what fraction of the target DNA fragments would fail to hybridize with a probe in the 2 hour annealing step." *Id.* He thus makes a "guess" that the fraction would be "1%" and that it would be sufficient to satisfy steps 1(a) and 1(b) if 1% of the target DNA fragments became attached to the beads while still single-stranded and thereafter formed double-stranded hybridization complexes with the oligos. *Id.*

Dr. Cooper's characterization of his "1%" estimate as no more than a "guess" demonstrates that it is speculative and unreliable. But setting that aside, in deposition, Dr. Cooper testified that the guess could be off by a hundred-thousand fold—or flatly wrong altogether. Indeed, in deposition Dr. Cooper testified that it is "possible" that the fraction actually could be ".00001 percent," Ex. 3 (Cooper Tr.) at 228:25-229:3, and that it is not "impossible" that "at some point there is essentially no unbound target sequence" available to practice the claim steps in the recited order. *Id.* at 229:15-230:3.

Dr. Cooper has not offered any non-speculative evidence that any percentage of single-stranded cfDNA in Harmony V2 binds to the beads in the sample (instead of first hybridizing with complementary oligos and then binding to the beads as a double-stranded hybridization complex).

[3] As explained in Ariosa's Motion for Summary Judgment, there would still be no infringement even in this scenario because step 1(a) is satisfied only where the sample begins with single-stranded target sequences *already attached* to a first solid support. Step 1(a) is not satisfied by performing a reaction in which single stranded target sequences are separately added into a sample and then become attached by virtue of a biochemical reaction.

He admitted it is not "impossible" that it never happens. *Id.* His "guess" that some fraction of the single-stranded cfDNA (ranging from .00001 percent to 1 percent) binds to the beads while remaining single-stranded is not a reliable scientific basis for offering an opinion that Harmony V2 satisfies step 1(a). Put simply, Dr. Cooper's opinion on this subject does not meet the Supreme Court's reliability requirements under *Daubert*.

Dr. Cooper admitted in his deposition that "[t]here was not a formal basis for making that guess." *Id.* at 217:17-18. Indeed, Dr. Cooper does nothing to link his "guess" to any actual measurement or other factual basis for estimating the fraction of single-stranded DNA in the sample that binds to the beads (instead of first hybridizing with complementary oligos and then binding to the beads as double-stranded hybridization complexes). In paragraph 241 of his report, Dr. Cooper purports to carry out a calculation to estimate the total number of single-stranded cfDNA sequences present in each starting sample in Harmony V2. Ex. 2 (Cooper Rpt.) at ¶ 241. But he does not in any way tie that number to the 1% "guess" he makes as to how many of those single-stranded cfDNA sequences bind to the beads while remaining single-stranded. *See id.* at ¶¶ 241-242.

Moreover, even if Dr. Cooper did now somehow try to tie his "guess" to the calculation of paragraph 241, it would be unavailing because the method by which he made his calculation in paragraph 241 is itself flawed and unreliable. For example, in deposition, Dr. Cooper admitted that he used the wrong molecule fragment length in his calculation. Ex. 3 (Cooper Tr.) at 222:9-16; *see also* 221:6-13. In fact, Dr. Cooper admitted in deposition that he made up the molecule fragment length used in his calculation because it was "a simplifying assumption" to "make[] some of the math a little simpler." *Id.* at 222:21-223:3. An expert opinion may not be based on assumptions of fact without evidentiary support. *See, e.g., Guidroz-Brault v. Mo. Pac. R.R. Co.*, 254 F.3d 825, 830-31 (9th Cir. 2001) (excluding expert testimony "not sufficiently founded on facts"). "When expert opinions are not supported by sufficient facts, or when the indisputable record contradicts or otherwise renders the opinions unreasonable, they cannot be relied upon." *W. Parcel Express v. United Parcel Serv. of Am., Inc.*, 65 F. Supp. 2d 1052, 1060 (N.D. Cal. 1998); *see also Estate of Gonzales v. Hickman*, No. 05-660-MMM, 2007 WL 3237727, at *3, n.34 (C.D. Cal. May 30,

2007) (expert "cite[d] no specific facts in the record . . . which support the opinion, and the only available evidence contradicts it. Consequently the court concludes the opinion is not admissible"); *United States v. Rushing*, 388 F.3d 1153, 1156 (8th Cir. 2004) ("Expert testimony should not be admitted when it is speculative, it is not supported by sufficient facts, or the facts of the case contradict or otherwise render the opinion unreasonable"); *Greenwell v. Boatwright*, 184 F.3d 492, 497 (6th Cir. 1999) ("Expert testimony . . . is inadmissible when the facts upon which the expert bases his testimony contradict the evidence").

In fact, Dr. Cooper did not even consider certain relevant facts in arriving at his "guess." For example, Dr. Cooper did not consider the actual molar excess of oligos[4] in the reaction of Harmony V2. Ex. 3 (Cooper Tr.) at 210:14-211:16. He admitted in deposition that molar excess is relevant because "if you're trying to get A to stick to B, then the more A you put in, the greater the likelihood that A sticking to B will occur…." *Id.* at 162:20-163:13. But Dr. Cooper admitted in deposition that, as far as the *actual* molar excess of oligos in Harmony V2, "[he] did not consider any specific estimate of what those concentrations might be." *Id.* at 211:5-11.

Moreover, Dr. Cooper admitted in deposition that he "can't really give you a [] precise or concrete error estimate" for the rate of error in his calculations or his "guess." Ex. 3 (Cooper Tr.) at 227:11-24. He did admit, however, that his "guess" could be off by as much as a hundred thousand-fold—or could be completely wrong altogether. *Id.* at 228:25-229:3 (admitting that it is possible that the fraction he "guess[es]" to be 1% could actually be ".00001%"); *id.* at 229:15-230:3 (admitting that it is not "impossible" that "at some point there is essentially no" molecules practicing the claim steps in the recited order); *see Daubert*, 509 U.S. at 594 (directing courts to consider the known or potential error rate of the scientific technique).

Dr. Cooper also provided no evidence that his methodology is generally accepted in the art. Dr. Cooper admitted in deposition that his methodology had never been peer reviewed. Ex. 3 (Cooper Tr.) at 230:4-8; *see Daubert*, 509 U.S. at 593 (instructing that a "pertinent consideration"

[4] Molar excess refers to the excess in relative amount of molecules of DANSR oligos as compared to cfDNA. A molar excess of oligos refers to a relatively higher concentration of DANSR oligos as compared to cfDNA molecules.

in determining the reliability of an expert opinion "is whether the theory or technique has been subjected to peer review" because "submission to the scrutiny of the scientific community is a component of 'good science'…"). He also did not provide a single citation or reference that used his technique in his expert report, and he admitted that, to his knowledge, his methodology has never been used by his peers. Ex. 3 (Cooper Tr.) at 230:9-21. There is no evidence that the methodology that Dr. Cooper used to make his "guess" would be accepted by the scientific community. *See, e.g., Competitive Techs., Inc. v. Fujitsu Ltd.*, 333 F. Supp. 2d 858, 881 (N.D. Cal. 2004), *aff'd*,185 F. App'x 958 (Fed. Cir. 2006) (precluding expert's estimates regarding inductance as speculative and because there was "no evidence suggesting that [expert's] methodology has been subjected to peer review or would be accepted in the relevant scientific community"); *Oxford Gene Tech. Ltd. v. Mergen Ltd.*, 345 F. Supp. 2d 431, 438 (D. Del. 2004) (precluding biomedical expert's opinion where the expert did not provide any basis, citation or support for the conclusion in his report).

Dr. Cooper's opinions at paragraphs 240-244 are nothing more than "unsupported speculation" that fail the *Daubert* test for reliability. *Daubert*, 509 U.S. at 590. "The report on its face does not articulate a reliable principle or method that could be explained or tested." *Brighton Collectibles, Inc. v. RK Tex. Leather Mfg.*, 923 F. Supp. 2d 1245, 1256 (S.D. Cal. 2013) (citing *Daubert*, 509 U.S. at 593-94) (further precluding expert's opinion and testimony because "[w]hen deposed, [expert] could not identify the factual basis for his assumptions or provide any assurance that his conclusion is based upon a method that is generally accepted in the field or that has a known margin of error that could be tested by other professionals"). "[T]here is simply too great an analytical gap between the data and the opinion proffered." *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

For at least these reasons, Ariosa respectfully requests that the Court grant its motion to exclude the referenced opinion and testimony of Plaintiffs' expert Dr. Gregory Cooper.

Dated: September 1, 2017

Respectfully submitted,

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By: */s/ Sandra L. Haberny*
Sandra L. Haberny
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